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Original Article

To Evaluate the Effect of Olmesartan on Blood Glucose Levels and Blood Lipid Levels in Streptozotocin Induced Diabetic Rats

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Abstract

Experimental Approach: Wistar albino rats were randomly selected and divided into 3 groups. Diabetes was induced by injecting Streptozotocin intraperitonelly. The control group received 1% Gum acacia (oral), standard group received 0.5 mg/kg Glibenclamide (oral) and the test group received Olmesartan 3.6 mg/kg body weight (oral) from 0-28 days respectively. Fasting blood glucose was estimated on 0, 1, 3, 7, 14, 21 & 28th day by (ACCUCHECK) glucometer and fasting lipid profile by lipid screening strips on 1st and 28th day.

Key Results: The blood glucose levels in the Olmesartan group was less when compared to the control group at all the intervals but comparable with that of glibenclamide. The Olmesartan group showed improved lipid profile when compared to control group in streptozotocin induced diabetic rats.

Conclusion and Implications: Olmesartan showed hypoglycemic activity and improved lipid profile action which is comparable to standard drug glibenclamide.

Introduction

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. DM is usually caused by a complex interaction of genetics, environmental, inflammation and autoimmune factors. The metabolic dysregulation and complications are associated with diabetes are due to glucotoxicity, lipotoxicity, formation of Advanced Glycation End Products (AGEs), Protein kinase C and Hexosamine pathway products, all these comprehensively causes secondary pathophysiologic changes in multiple organ systems

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that impose a tremendous burden on the individual with diabetes and on the health care system (1, 2, 3).

Newer targets of angiotensin receptor blockers (ARB's) in diabetes mellitus:

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium (4).

Action of angiotensin II through AT_1 receptor:

Angiotensin II acting through AT_1 receptor increases the synthesis and concentration of tumor necrosis factor α, interleukin6, IL-1, chemokine monocyte chemo attractant protein1 and nuclear factor kappa of activated B cells (NFκB) which results in inflammatory cell infiltration in β cells and is important in the pathogenesis of type 2 diabetes. These inflammatory cytokines are important in the pathogenesis of lipid metabolism also. IL-6 and IL-1 act on the liver to produce the characteristic dyslipidemia of the metabolic syndrome, with increased VLDL and decreased HDL. IL-1β is known to activate the Inhibitor of $\kappa\beta$ (I$\kappa\beta$) and induce insulin resistance. Hence, Angiotensin II through AT_1 receptor can advance the occurrence of Diabetes or insulin resistance by above said mechanisms.

Action of adiponectin and adipokines:

Obesity causes inflammation particularly central obesity (mesenteric fat) (LTB4 an inflammatory molecule) which in turn can lead to type 2 diabetes by releasing inflammatory cytokines from the mesenteric adipocytes. Extra fat particularly in the liver and mesentery activates the resistant macrophages and immune cells. When these macrophages are activated release LTB4 and other immune signaling molecules to influx of new macrophages as a positive feedback loop, the newly arriving macrophages also get activated and release more LTB4. When inflammation is chronic as in case of obesity and the LTB4 starts activating other cells Fig. 1.

Macrophages of liver, fat (more so in mesenteric fat) and skeletal muscle cells also have LTB4 receptors on their surfaces and are activated when LTB4 binds to them. In obesity these cells become inflamed and release adipokines leading to insulin resistance (5).

Adipocytes secrete a number of biological products (adiponectin, non-esterified free fatty acids, retinol binding protein 4, leptin, TNF-α and resistin). Adipocytes products or adipokines produce an inflammatory state, these adipokines modulate insulin sensitivity and cause insulin resistance in skeletal muscles and liver and may explain why markers of inflammation as IL6 and C-reactive protein are often elevated in type 2 diabetes (6). Adiponectin acts as an insulin sensitizing peptide is reduced in Diabetes

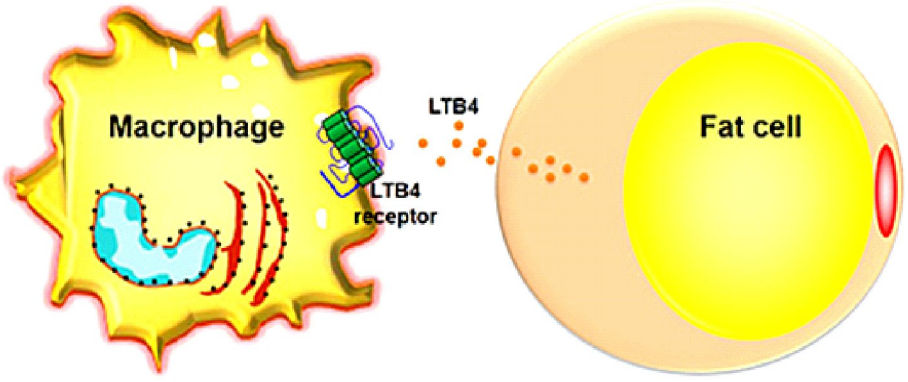

Fig. 1: Release of adipokines.

and this may contribute to insulin resistance (7).

Adiponectin belongs to the family of adipocytokines, is exclusively synthesized by white adipocytes, and is induced during adipocyte differentiation. Adiponectin plays a role in regulation of glucose metabolism, lipid metabolism, inflammation and oxidative stress. Hence, adiponectin plays a role in lowering blood glucose and blood lipid levels (8).

Adiponectin has 2 receptors

1. Adipo R1 – skeletal muscle

2. Adipo R2 – Liver

These two adiponectin receptors are predicted to contain seven transmembrane domains but to be structurally and functional distinct from G-protein coupled receptors. Expression/suppression of AdipoR1/R2 by small interfering RNA serve as receptor for globular and full length adiponectin and they mediates AMP kinase, PPAR γ and PPAR-α ligand activities as well as fatty acid oxidation and glucose uptake (9, 10).

Molecular mechanism underlying the insulin sensitizing action of adiponectin, indicates that stimulation of glucose utilization and fatty acid combustion by adiponectin, through activating AMPK (5' Adenosine Monophosphate kinase) and there by directly regulating glucose metabolism and insulin sensitivity (11).

Improved hepatic insulin sensitivity occurs, leading to postulate that the primary effects of adiponectin on muscle are to augment uptake and combustion of free fatty acids (FFAs), whereas decreased liver triglyceride content results from secondary reduction in serum FFA and triglyceride levels Fig. 2.

Hence angiotensin II activity through AT_1 receptor will decrease the production of adiponectin and increase the inflammatory adipokines by which

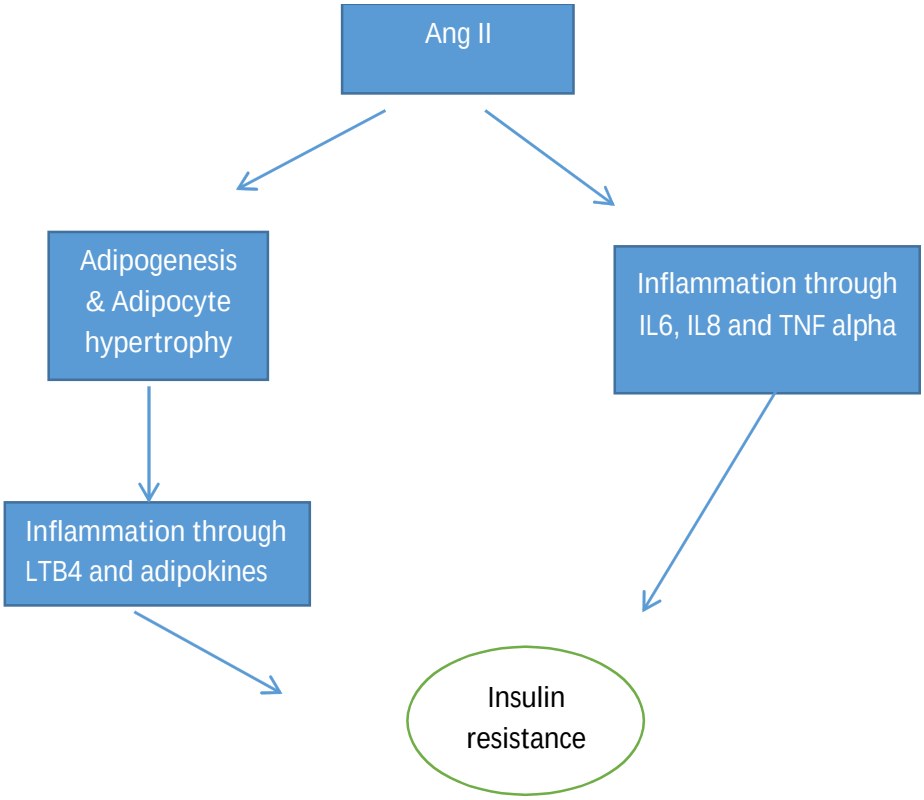

Fig. 2: Mechanism of insulin resistance.

contributing to one of the factor of insulin resistance and diabetes. Thus, Angiotensin II acting through AT_1 receptor at various places of its target like â cells, hepatic tissues, adipose tissues (skeletal muscle tissue) possibly influence aggravation or initiation of diabetic status.

Angiotensin receptors blockers reduce inflammation, regulate cell growth, apoptosis, decreasing fibrosis, decreasing collagen deposition etc. of β cell, skeletal muscle cell and adipose tissue. These are expressed because it increases adiponectin directly by inhibiting the activation of AT_1 receptors by angiotensin II and also mediated by PPAR-γ and AMP (5' Adenosine Monophosphate) activated protein kinases. Olmesartan is a partial PPAR α agonist and induces PPAR α expression. Thus there is induction of hepatic ACSL1 (Acyl CoA Synthetase Long chain) and CPT1A (Carnitine Palmitoyl Transferase). This causes significant decrease of triglyceride level.

Thus, angiotensin II receptor inhibition through Olmesartan has blood glucose lowering effect and also lowers triglyceride levels, total cholesterol levels, LDL levels and raise HDL levels, by inducing adiponectin protein expression, via PPAR γ, AMP kinases activation and decreasing the inflammatory response of IL1, IL6, TNF-α etc. Lipid lowering effect by PPAR α expression, induction of hepatic ACSL1 (Acyl CoA Synthetase Long chain), CPT1A (Carnitine Palmitoyl Transferase) and reduction in catecholamine levels (noradrenaline).

Hypothesis:

Thus it may be hypothesized that Olmesartan decrease the blood sugar level and lipid level through its activity of blocking action of angiotensin II on AT_1 receptor and promoting the activity of adiponectin and decreasing the activity of adipokines.

Methods

The study was conducted at Central Animal Facility and all animals care and experimental protocols were approved by the Institutional Animal Ethics Committee (*IAEC)*.CPSEA approval number from IAEC of: JSSMC/IAEC05/5657/DEC 2013.

Wistar albino rats of either sex of average weight 150-200 gms aged 3-4 months were used in the experiments. The rats were inbred in the central animal house, under suitable conditions of housing, temperature, ventilation and nutrition. Rats were housed two to three per stainless cage under conventional conditions. They were kept at a constant temperature of 26±2°C and relative humidity of 30-70% under a 12 h dark/light cycle. Food and water were available *ad libitum*. The rats were acclimatized to the laboratory conditions for seven days prior to test before assigning animals to treatment group. The doses of drugs were based on human daily dose converted to that of rats according to Paget and Barnes (1962). The method employed in this study to induce diabetes was chemical method using streptozotocin, given intraperitoneally. Blood glucose estimation was done by using glucometer.

Drugs and Chemicals: Glibenclamide (*Sanofi Aventi, India),* Olmesartan (*Macleods, India),* Streptozotocin *(Sisco Research Laboratories Pvt. Ltd. India).* The rats were divided into 3 groups containing six animals (n=6) in each group (control, standard and test group).

Induction of diabetes:

Following an overnight fast, 24 rats were injected intraperitonally, with freshly prepared Streptozotocin (dissolved in sodium citrate buffer) under aseptic precautions in a dose of 55 mg/kg body weight. Animals were carefully observed for first 24 hours following the injection for any evidence of allergic reactions, behavioural changes, convulsions and hypoglycemic attacks. No untoward reactions were observed in any animal.

Blood glucose level was recorded daily morning at 9.00 am for 3 days. Animals which developed stable hyperglycemia on 3rd day with blood glucose level more than 2500 mg/L were selected for the study. They were randomly grouped as Diabetic control, Diabetic standard, Olmesartan group. All the drugs were given for 28 days.

Group 1: Diabetic control: 1% Gum acacia (PO)

Group 2: Standard: 0.5 mg/kg body weight, Glibenclamide (PO)

Group 3: Olmesartan: 3.6 mg/kg body weight (PO).

- Blood was collected from 12 hr fasted rats by rat tail vein puncture method, 1hr after each dose administration of the respective drugs and fasting blood glucose was estimated by (ACCUCHECK) glucometer on 0, 1, 3, 7, 14, 21 & 28th day.
- Body weight of the individual rats was measured on the respective days before blood glucose estimation on 0, 1, 3, 7, 14, 21 & 28th day.
- Estimation of fasting lipid profile by lipid screening strips on 1st and 28th day.

Statistical analysis:

The results was analyzed Mean and standard deviations were calculated for each group. One way ANOVA was used for multiple group comparisons followed by post hoc Tukey's test for statistical significance between groups. IBM SPSS statistics ©IBM Corporation and Other(s) 1989, 2012 software was used for statistical analysis purpose. $P<0.05$ was considered as significant.

Results

The diabetic control rats showed progressive hyperglycemia and the standard drug showed persistent decrease in the blood glucose level from 1st to 28th day, while the test drug, Olmesartan did not show appreciable decrease in blood glucose levels from 1st to 3rd day but thereafter produced consistent decrease in blood glucose levels upto 28th day. There was reduction in CBG level of Standard and Olmesartan group which was very minimal on 1st day but started producing consistently progressive fall in CBG level from day 3-day 28. Week wise comparison in blood glucose level showed that the Olmesartan group showed lesser reduction in the first week compared to the standard. At the end of second week standard continued similarly but there was continued fall in the test group. At the end of 4th week both Olmesartan and standard almost performed same activity.

There was a gross increase in total cholesterol, triglyceride and LDL level in diabetic control but the level of total cholesterol was very minimal with respect to standard, whereas there was moderate increase in total cholesterol with respect to Olmesartan. There was gross decrease in HDL level in diabetic control group. The fall in HDL was very minimal with standard. The decrease in HDL was very minimal with Olmesartan (better than standard).

In diabetic control group, there was reduction of 20% body weight and in standard group 7% increase in body weight. In the Olmesartan group there was 3.53% increase in the body weight.

Discussion

Angiotensin II exerts several cytokine like actions via the AT1 receptor and can stimulate multiple signalling pathways, activate several growth factor receptors, and promote the formation of reactive oxygen species (ROS) and other proinflammatory responses (12).

Angiotensin II, have a potential role in endothelial cell dysfunction, insulin resistance, inammation, and proliferative effects (13). Insulin resistance of Angiotensin II is by interfering with the insulin-stimulated increase in insulin receptor substrate 1-associated PI3K activity (14). Angiotensin II also stimulates the production of superoxide radicals, TGF-β, endothelin, and plasminogen activator inhibitor (PAI-1), which ultimately interferes in NO action (15).

The main insulin-sensitizing action of adiponectin results from decrease in hepatic gluconeogenesis and increase in muscle glucose transport and, secondly from enhancement of energy consumption and fatty acid oxidation in peripheral tissues with the aim of increasing ATP production. Accumulating evidence from clinical, experimental animal and genetic studies support a close association between hypoadiponectinemia and insulin resistance/ type 2 diabetes (16).

The primary effects of adiponectin on muscle are to

augment uptake and combustion of free fatty acids (FFAs), whereas decreased liver triglyceride content results from secondary reductions in serum FFA and triglyceridelevels (17).

The induction of adiponectin in fact might be caused by secondary effects involving other PPAR- inducible genes and not by specific activation of the PPAR response elements (18).

The strong inverse correlation between serum adiponectin levels and intra-abdominal fat mass may in part underlie the link between visceral fat and insulin resistance (19).

Olmesartan has been applied most frequently because of having partial peroxisome proliferator-activated receptor gamma (PPARγ) agonist activity (20).

The possible mechanisms by which ARBs may improve the insulin resistance are hemodynamic effects, increase of glucose transport and improvement of the intracellular signal transduction of insulin, through the blockade of Ang II and inhibition of oxidative stress. (21, 22, 23).

Angiotensin receptor blockers have a partial agonist action of PPARγ and are expected to have beneficial effects on insulin resistance by increasing adiponectin levels.

In the present study, the standard group treated with glibenclamide (0.5 mg/kg) showed a steady decrease in blood glucose levels from 3588 mg/L on Day 0 before administration of drug to 1736.6 mg/L on day 28 thus indicating that the standard drug has a good immediate and also prolonged hypoglycemic action. Diabetic Olmesartan group decreased blood glucose level from 3553.3 mg/L on day 0 to 2008.3 mg/L on day 28. The difference in the blood glucose readings between D0 to D28 for Olmesartan group is 1545 mg/L. The control group treated with gum acacia increased the blood glucose level from 3511 mg/L on day 0 to 4388 mg/L on day 28.

The progressive consistent hypoglycemic effect with respect to duration of administration and maximum effectiveness of the test drug was seen after 1st week, but persistent continued hypoglycemic activity was continued up to end of 4 weeks. At the end of study the percent reduction of blood glucose level in Olmesartan group was 54.23% when compared to diabetic control, while, 16.57% decrease in blood glucose level when compared to Standard (Glibenclamide) group and has shown similar reduction in mean percent blood glucose level, and it was statistically significant ($p<0.005$) compared to diabetic control group. This indicate that Olmesartan has significant and sustained hypoglycemic activity persisting till last day (28th day) compared to standard in their respective experimental dosages. The above data conclude that Olmesartan has the capacity to improve the glycemic status in experimentally induced diabetes in animals and the glycemic status of test drug is almost equal to that of standard at all-time intervals (Table I).

In diabetic control there was a gross increase in total cholesterol (93.17 mg/L), triglyceride (1088.3 mg/L) and LDL level (858.3 mg/L), whereas there was gross decrease in HDL level (101.7 mg/L) compared to both standard and test group from 0-28 day. While, the test drug Olmesartan also showed moderate increase in total cholesterol (313.4 mg/L), triglyceride (540 mg/L) and LDL levels (386.7 mg/L)

Table I: Blood glucose levels in different groups.

	Groups	*D0*	*D1*	*D3*	*D7*	*D14*	*D21*	*D28*
1	Diabetic control	3511.6±118.0	3703.3±158.5	3821.6±20.15	3893.3±238.2	4055±227.9	4206.6±237.6	4388.3±257.6
2	Standard	3588.0±159.4	3516.6±212.7	3273.3±17.52	3013.3±190.7	2655±227.5	2001.6±247.0	1736.6±244.8
3	Olmesartan	3553.3±186.9*	3518.3±205.3*	3251.6±23.04*	3025.0±183.9*	2713.3±100.1*	2308.3±241.6*	2008.3±220.6*

Data expressed in Mean mg/L ± SD values. *P<0.05 compared with control.
D0 = before giving the drug.
D1, D3, D7, D14, D21, D28 = 1st, 3rd, 7th, 14th, 21st, 28th days of administration of the drugs respectively.

from 0-28 day when compared to control. The decrease in HDL levels of Olmesartan was 66.6 mg/L from 0-28 day. Olmesartan was inferior to standard (60 mg/L) in reducing the total cholesterol from 0-28 days. Olmesartan was inferior to standard (76.7 mg/L) in reducing the triglyceride levels from 0-28 days. Olmesartan was inferior to standard (26.7 mg/L) in reducing the LDL levels from 0-28 days. Olmesartan was inferior to standard (23.3 mg/L) in increasing the HDL levels from 0-28 days. Thus to conclude the test drug Olmesartan is better in improving the lipid profile compared to control and is comparable with that of standard (Table II, III, IV and V).

As a consequence of induction of diabetes by Streptozotocin there was significant reduction in body weight in the control group of rats between 0-28 days. In the standard group of rats there was no reduction in the body weight rather there was slight improvement in weight from 0-28 days but in the Olmesartan group there was no much change in the body weight between 0-28 day of experimentation (Table VI). Improved body weight of the treated animals indicates the efficacy of Olmesartan in controlling the glucose excretion and blood glucose level of diabetic rats. The activity and behavior of diabetic control was less and gradually decreased from 0-28th day but the activity and behavior was almost normal throughout the study in standard and Olmesartan group.

Conclusion

Thus, the hypothesis put forth in the beginning, the glucose lowering effect of Olmesartan was through the mechanism like inducing adiponectin protein expression, via PPAR γ activation, AMP kinases activation, decreasing the inflammatory response of IL1, IL6, TNF-α and reduction in catecholamine levels (noradrenaline). Lipid lowering effect of Olmesartan was through PPAR α expression, induction of hepatic ACSL1 (acyl coA synthetase long chain), CPT1A (carnitine palmitoyl transferase).

Hence the present study establishes the hypoglycemic activity of Olmesartan group when

TABLE II : Statistical Analysis showing comparison of Total cholesterol levels between different groups on day 1 and day 28.

Groups	*Mean±SD on 1st day*	*Mean±SD on 28th day*	*Difference in TC levels*
Diabetic control	1193.3±107.8	2125±81.1	931.7±26.7
Standard	1066±77.6	1006±78.9	60±1.3
Olmesartan	1141.6±76.0*	1455±58.2*	313.4±17.8*

Data expressed in Mean mg/L±SD values. *P<0.05 compared with control.

TABLE III : Statistical Analysis showing comparison of Triglyceride levels between different Groups on day 1 and day 28.

Groups	*Mean±SD on 1st day*	*Mean± SD on 28th day*	*Difference in TG levels*
Diabetic control	1013.3±143.4	2101.6±144.6	1088.3±1.2
Standard	1095±145.5	1018.3±53.4	76.7±92.1

TABLE IV : Statistical Analysis showing comparison of LDL levels between different Groups on day 1 and day 28.

Groups	*Mean±SD on 1st day*	*Mean± SD on 28th day*	*Difference in LDL levels*
Diabetic control	1278.3±101.4	2136.6±91.1	858.3±10.3
Standard	1113.3±98.9	1140±107.5	26.7±8.6
Olmesartan	1203.3±35.5*	1590±50.1*	386.7±14.6*

Data expressed in Mean mg/L±SD values. *P<0.05 compared with control.

TABLE V : Statistical Analysis showing comparison of HDL levels between different Groups on day 1 and day 28.

Groups	*Mean±SD on 1st day*	*Mean± SD on 28th day*	*Difference in HDL levels*
Diabetic control	373.3±52	271.6±42.6	101.7±9.4
Standard	423.3±30.7	446.6±36.1	23.3±5.4
Olmesartan	401.6±38.6*	335.±39.3*	66.6±0.7*

Data expressed in Mean mg/L±SD values. *P<0.05 compared with control.

TABLE VI : Table showing mean values of body weight of rats in different groups on different days.

Groups	*Before STZ*	*D0*	*D1*	*D3*	*D7*	*D14*	*D21*	*D28*
Diabetic control	215	169	172	153	161	159	171	173
Standard	200	182	173	181	192	189	201	214
Olmesartan	198	170	160	155	178	188	192	205

Values in grams.

compared to control, which is statistically significant ($p<0.05$) and comparable to standard drug Glibenclamide in Streptozotocin induced diabetic rats. Also, Olmesartan shows less improved lipid profile action when compared to control, which is statistically significant ($p<0.05$) and comparable to standard drug Glibenclamide in Streptozotocin induced diabetic rats.

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Nil

Conflict of interest

Nil

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